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09/622,646	08/21/2000	Yasuko Ozaki	053466/0286	8792

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/622,646	OZAKI ET AL.	
	Examiner	Art Unit	
	Christine Foster	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 October 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4 and 6-17* is/are pending in the application.

4a) Of the above claim(s) *3,4,10-12 and 14-16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,6-9,13 and 17* is/are rejected.

7)☒ Claim(s) *1, 17* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 August 2000 and 19 September 2008* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Notice to Comply*.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/18/07 has been entered. The supplemental amendment filed on 9/19/2008 is further acknowledged.

Election/Restrictions

2. Applicant's election with traverse of Group I, claims 1-2, 6-9, 13 and 17 in the reply filed on 4/29/08 is acknowledged. The election of species (a), protein having the amino acid sequence modified by lacking 17 amino acid residues from the C-terminal of SEQ ID NO:1 (now SEQ ID NO:20), but not lacking 27 amino acid residues from the N-terminal, is further acknowledged. The traversal is on the ground(s) that the claims of Group II are sufficiently related so as not to constitute an undue search burden. This is not found persuasive because in the instant case, each of the species requires a separate analysis for compliance under 35 U.S.C. 112, 1st paragraph. In addition, the different protein species require separate analysis for prior art purposes, thereby presenting an additional burden of examination.

The requirement is still deemed proper and is therefore made FINAL.

3. Claims 3-4 and 15-16 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 4/29/08.

Status of the Claims

4. In the Reply of 10/18/07, claims 1 and 3 were amended. New claim 17 was added. Claims 1, 3, and 17 were further amended in the supplemental Reply of 9/19/08. Accordingly, claims 1-4 and 6-17 are pending in the application with claims 3-4, 10-12, and 14-16 currently withdrawn. Claims 1-2, 6-9, 13, and 17 are subject to examination below.

Priority

5. The present application was filed on 8/21/00 and is a national stage (371) entry of PCT/JP99/00885, filed 2/25/99. Acknowledgment is also made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d) to Application No. 10-60613, filed on 2/25/98 in Japan.

6. Receipt is acknowledged of papers submitted on 2/22/2008 under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

Objections/ Rejections Withdrawn

7. The rejections of claims 3-4 and 15-16 as set forth in the Final Office action mailed 5/4/2007 have been withdrawn in view of the withdrawal of these claims as discussed above.

8. The rejections of claims 1-2, 6-9, 13, and 17 under § 103 as being unpatentable over Goto et al. as set forth in the Final Office action mailed 5/4/2007 have been withdrawn pursuant to further consideration by the Examiner in favor of the rejections set forth below under § 102.

Specification

10. The specification is objected to for the following reasons:

11. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1 .821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1 .821 through 1 .825 for the reason(s) set forth on the attached *NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES*. As previously indicated (see the Notice to Comply mailed on 8/19/2008), each sequence identifier should be used to identify a single, unique sequence and not multiple sequences.

12. In addition, pages 71-73 of the specification describe Applicant's amendment of 9/19/08 includes amendments to pages 71-73 of the specification (see the amendment at pages 8-9). These amendments refer to SEQ ID NOs 1-19 but suggest that each of these SEQ ID NOs identifies both an amino acid sequence as well as a nucleotide sequence. As discussed above, this is improper as a single sequence identifier should only be used to identify a single sequence. Appropriate correction is required.

13. The use of the trademarks BIOMEK™, SPECTRAmax™ has been noted in this application (see, e.g., page 29, line 32; page 30, line 22). They should be capitalized wherever they appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Objections

14. Claims 1, 7-8 and 17 are objected to because of the following informalities:

15. Claims 1 and 17 recite "a protein having the amino acid sequence modified by lacking…residues from C-terminal in the amino acid sequence **shown in** SEQ ID NO:20" The terminology "shown in" is vague and may present confusion.

16. Claims 7-8 recite "wherein the anti-HM1.24 antibody bound to the soluble HM1.24 antigen protein or the soluble HM1.24 antigen protein bound to the anti-HM1.24 antibody is detected or determined" (emphasis added). The claims are objected to because the two alternatives recited are apparently the same, such that the claims are redundant and may present confusion.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

17. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

> pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

18. Claims 1-2, 6-9, 13, and 17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are currently being evaluated in light of the elected species of *a protein having the amino acid sequence modified by lacking 17 amino acid residues from the C-terminal of SEQ ID NO:20* as recited in parts (a) of claims 1 and 17. The analysis below is therefore directed only to this elected species.

The specification does not disclose "*a protein having the amino acid sequence modified by lacking 17 amino acid residues from the C-terminal of SEQ ID NO:20"* as such. The claims lack written description because there is insufficient direction in the original specification to the genus of proteins now claimed.

This terminology encompasses a genus of proteins that comprise a modified form of SEQ ID NO:20. In particular, "the amino acid sequence modified by lacking 17 amino acid residues from the C-terminal" would encompass not only the protein in which the last 17 amino acid residues SEQ ID NO:20 were removed, but also any protein lacking 17 amino acid residues anywhere in the C-terminus of the protein. When the claims are given their broadest reasonable interpretation, the residues removed need not be the last 17 residues; nor are they necessarily 17 consecutive residues.

It also is noted that the instant specification does not provide a specific or limiting definition for the "C-terminal". As such, this terminology could broadly refer to the last half of the protein, the last secondary structural domain, etc.

In addition, the use of open transitional language ("a protein **having**…") indicates that the protein may have additional residues on either end of the modified SEQ ID NO:20. In fact, although the claim refers to the sequence modified by lacking 17 amino acid residues, the use of open transitional language suggests that the protein may in fact contain additional unrecited residues. When the claims are given their broadest reasonable interpretation, therefore, the claimed protein could in fact comprise all of the amino acids in SEQ ID NO:20 and would also read on the full-length HM1.24 antigen.

The claims also require that the claimed genus of proteins possess certain functional characteristics, namely that the HM1.24 antigen protein is "**soluble**". As discussed in detail in the rejection under 35 U.S.C. 112, second paragraph below, the term "soluble" has not been assigned a specific or limiting definition in the instant specification.

As detailed below, different researchers have employed the terminology "soluble" to refer to different, non-coextensive properties of a protein. This could refer to the ability of a protein to dissolve in a solute (such as water). Alternatively, this could refer to a protein that is not membrane-bound, e.g. as the extracellular domain of an integral membrane protein.

However, even integral membrane proteins may be made soluble; and conversely non-membrane-bound proteins are not necessarily soluble but may form aggregates or precipitates.

The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter

later claimed. The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the application. These include "level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention." MPEP 2163.

The specification discloses that "the amino acid sequence as set forth in SEQ ID NO: 20 may be modified by deletion of one or more than one, preferably one or not greater than 42, and more preferably one or not greater than 17 amino acid residues" (page 8, lines 3-7; see the amendments to the specification of 9/19/2008[1]).

This passage therefore introduces the concept of removing 17 amino acids from SEQ ID NO:20. However, there is no direction here as to *which* 17 amino acids to remove; and in particular no direction to remove any 17 amino acids from the "C-terminal" of the protein (e.g., from the second half of the protein). The Examiner was unable to find any clear description of a protein corresponding to SEQ ID NO:20 with 17 amino acids removed (e.g., with the last 17 amino acids removed).

The specification also discloses the 147-amino acid protein SEQ ID NO:6, in which the last 17 residues of SEQ ID NO:20 are lacking (see Examples 14-15 and the sequence listing). However, the disclosure of SEQ ID NO:6 would at best represent a species reading on the now-claimed genus of proteins *"having the amino acid sequence modified by lacking 17 amino acid residues from the C-terminal of SEQ ID NO:20.*

[1] The original specification referred to "the amino acid sequence as set forth in SEQ ID NO: 1" rather than SEQ ID NO:20. However, the original sequence listing presented both the nucleotide and corresponding amino acid sequence information under the sequence identifier SEQ ID NO: 1. It can be seen in the original sequence listing filed on 8/21/200 that the amino acid sequence listed in SEQ ID NO: 1 is the same as that of SEQ ID NO: 20.

In particular, although SEQ ID NO:6 is disclosed to be "soluble", one skilled in the art cannot envisage what other proteins falling within the scope of the claimed genus would also be soluble.

Protein solubility was recognized in the art to be unpredictable. See Schimerlik et al. ("Overview of Membrane Protein Solubilization", Unit 5.9 In: Current Protocols in Neuroscience (February 1998), John Wiley & Sons, Inc., pages 5.9.1-5.9.5), which discusses how solubilizing membrane proteins is "***largely a matter of trial and error and depends on the protein of interest***" (see page 5.9.1, first paragraph).

It is known that even minor changes to an amino acid sequence can have dramatic effects on protein solubility. Pande et al. teach that a single point mutation leads to the aggregation of γD-crystallin (abstract; page 2947, right column, last paragraph; page 2498, "Conclusions"). Pande et al. also report the case of α-synuclein, in which a single point mutation (A53T) has been associated with Parkinson's disease in humans, but is found in several homologs of α-synuclein without pathologic effects (page 2947, right column, first full paragraph).

Tsitrin et al. ("Conversion of a transmembrane to a water-soluble protein complex by a single point mutation" Nat Struct Biol. 2002 Oct;9(10):729-33), who employ the term "soluble" to mean not membrane-associated, found that a single point mutation in the pore-forming toxin aerolysin converted this normally membrane-embedded toxin into a soluble protein (see especially the abstract).

Although the protein consisting of SEQ ID NO:20 *per se* is disclosed to be "soluble", the specification does not describe with any particularity what residues can be added to or removed from SEQ ID NO:20 while still maintaining solubility. When taken together with the

unpredictability in the art, the specification fails to convey evidence of possession of the claimed methods involving a genus of soluble proteins, as there is no disclosed correlation between structure and function (solubility). Of the large number of proteins that would "[have] the amino acid sequence modified by lacking 17 amino acid residues from C-terminal in the amino acid sequence shown in SEQ ID NO:20", it cannot be envisaged or predicted based on the disclosure which of these would be "soluble". As such, the skilled artisan cannot envisage the identities of the members of the genus.

An additional functional characteristic that is also required of the claimed genus is the ability to bind to anti-HM1.24 antibodies.

It is known that the loss of even a single hydrogen bond can profoundly affect the ability of an antibody to bind to its cognate antigen (see Harlow, E. and Lane, D., Antibodies: A Laboratory Manual (1988) Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, pages 23-26, see especially at page 26, the first full paragraph). The claimed genus is subject to significant variability, yet the specification does not indicate what additions or deletions to SEQ ID NO:20 can be made while preserving the ability of the protein to bind to antibodies that recognize native HM1.24. As above, there is no disclosed correlation between structure and function.

Therefore, although it may be routine to make changes to a peptide's amino acid sequences, because the functional consequences of such changes cannot be predicted, one skilled in the art cannot envisage which proteins "having the amino acid sequence modified by lacking 17 amino acid residues from C-terminal in the amino acid sequence showin in SEQ ID NO:20" would retain the ability to bind antibodies.

Accordingly, it is deemed that the specification fails to provide adequate written description for the genus of the claims and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

19. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

20. Claims 1-2, 6-9, 13, and 17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

21. Claims 1-2, 7-8, and 17 recite a "**soluble**" HM1.24 antigen protein. The term "soluble" has not been assigned a specific or limiting definition in the instant specification. Multiple plausible constructions of this term are possible, as different researchers have employed this terminology to refer to different, non-coextensive properties of a protein.

For example, Creighton et al. Creighton, T.E. ("Proteins: Structures and Molecular Properties" Second Edition, W.H. Freeman and Company, New York, (1993), pages 262-264) refer to the aqueous solubility of proteins in water, i.e. their ability to dissolve as opposed to proteins that exist as solids, aggregated into complexes (see section 7.1.1, in particular at page 262).

By contrast, Hale et al. (U.S. 2002/0069421A1) define "soluble protein" to refer to "any protein that is not an integral part of or closely associated with a cell membrane" [0030].

Similarly, Jiang et al. (US 2004/0168215 A1) employ the term "soluble" to refer to proteins without membrane attachments [0007].

These two constructions are not co-extensive because it is possible proteins not associated with a cell membrane can still be insoluble in aqueous solution.

For example, Prusiner et al. (U.S. 6,214,366 B1) teach that the normally soluble proteins such as Aβ peptide, α-synuclein, Tau, superoxide dismutase, huntingtin, and prion proteins (which are not membrane proteins) can be converted into an insoluble state (column 1, lines 11-61). Therefore, while such proteins would be considered according to the definition of Hale et al., they would not be considered soluble according to other definitions.

Conversely, integral membrane proteins may be solubilized by techniques that do not involve removal of their hydrophobic membrane-spanning regions. See Metz et al. (U.S. 5,370,996) at column 5, lines 1-13. Similarly, Schimerlik ("Overview of Membrane Protein Solubilization", Unit 5.9 in: Current Protocols in Neuroscience (February 1998), John Wiley & Sons, Inc., pages 5.9.1-5.9.5) discuss how membrane proteins can be solubilized or extracted from the membrane in aqueous solution (the abstract).

The specification does not make clear whether Applicant intends the term "soluble" to refer to aqueous solubility, to exclude transmembrane or membrane-associated proteins, or to encompass both of these. Because the HM1.24 antigen is a membrane-associated protein, either of these two constructions would be plausible interpretations of the claim term. For these reasons, the metes and bounds of the claim cannot be determined.

In addition, protein solubility is dependent on a number of factors. Considering the term "soluble" as it is used by Creighton to refer to a protein's ability to dissolve, it is noted that a

protein may be "soluble" in one solvent (e.g., in aqueous solvent) but insoluble in a different buffer system (e.g., in the presence of organic solvent or detergents) and vice versa. See Engel et al. (U.S. 7,319,021 B2) at column 8, lines 49-52). As taught by Creighton et al., protein solubility also depends on pH (paragraph bridging pages 262-263) and on the presence of cosolvents such as salts, organic solvents, and polymers (page 263, last paragraph to page 264). Solubility may also be temperature-dependent (see Pande et al., page 2494, right column, last paragraph).

As a result, the reference to "soluble" HM1.24 antigen protein also renders the claims indefinite because it refers to an object that is variable, namely the type of solvent in which the protein is dissolved or even the temperature of the system. See MPEP 2173.05(b).

22. Claim 1 recites "a protein having the amino acid sequence **modified by lacking 17 or 14 amino acid residues from C-terminal in the amino acid sequence shown in SEQ ID NO:20**" (emphasis added). Similarly, claim 17 recites "a protein having the amino acid sequence **modified by lacking 17 amino acid residues from C-terminal in the amino acid sequence shown in SEQ ID NO:20**". This terminology could be interpreted as meaning that the protein is modified by removal of the last contiguous 17 amino acids of SEQ ID NO:20. However, when the claims are given their broadest reasonable interpretation, "residues from C-terminal" could also mean that 17 residues are removed from the C-terminal region of the protein, but not necessarily the last 17 residues or the last contiguous residues. For example, this could refer to a protein in which a sequence of 17 residues within the last half of the protein is removed, but not necessarily the last 17 residues; or to a protein in which 17 non-contiguous residues within the last half of the protein are removed.

In addition, the specification does not provide a specific or limiting definition for the term "C-terminal". Different researches may employ this same terminology to refer to different sets of amino acids. For example, the C-terminus may refer to the last half of the protein. Alternatively, this could refer to the last secondary structure domain. Without a specific definition, it cannot be determined based on the specification which residues would be considered to represent the "C-terminal residues". This causes difficulty in ascertaining the scope of the claim, as a particular residue might be considered by one researcher to be in the "C-terminal" yet not by another. For all of these reasons, the metes and bounds of the claim is unclear.

23. Claims 9 and 12 recite "biotin/avidin", which is vague and indefinite because it is unclear whether Applicant intends that the antibody is labeled with biotin or avidin, or alternatively with biotin and avidin, etc.

Claim Rejections - 35 USC § 102

24. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

25. Claims 1, 7, 13, and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Goto et al. ("A novel membrane antigen selectively expressed on terminally differentiated human B cells" Blood. 1994 Sep 15;84(6):1922-30 and as evidenced by Schimerlik ("Overview of

Membrane Protein Solubilization", Unit 5.9 in: Current Protocols in Neuroscience (February 1998), John Wiley & Sons, Inc.).

Goto et al. teach an immunoprecipitation assay method comprising the steps of reacting soluble HM1.24 antigen protein and an anti-HM1.24 antibody and determining the amount of binding by autoradiography (see page 1924, right column, "Immunoprecipitation"; page 1927, right column, last paragraph to page 1928, first paragraph; and Figure 5 and legend).

With respect to the limitation that the HM1.24 antigen protein is "soluble", Goto et al. solubilized RPMI 8226 plasma cells expressing the HM1.24 antigen, which is a cell-surface membrane antigen (see also the abstract and page 1922, left column, second paragraph to right column, first paragraph). This means that the solubilized cell preparation included solubilized HM1.24 antigen (as confirmed by the autoradiography data of Figure 5).

Additional evidence that the HM1.24 in the cell preparation of Goto et al. is "soluble" is found in Schimerlik, who discuss the process of solubilization of membrane proteins by dispersal in aqueous solution (see in particular the abstract). Absent a specific or limiting definition for the terminology "soluble" in the instant specification, therefore, the HM1.24 protein of Goto et al. would be considered "soluble" when this terminology is given its broadest reasonable interpretation as the protein of Goto et al. was dispersed in aqueous solution (lysis buffer).

Goto et al. is silent regarding the amino acid sequence information for the HM1.24 protein detected. However, the instant specification specifically refers to the results of Goto et al. (page 1, lines 14-23) and indicates that the HM1.24 antigen expressed on the cell membrane has the amino acid sequence of SEQ ID NO:26, depicted in Figure 14 (specification, page 6 and the sequence listing filed on 9/19/2008). Based on this disclosure, it appears that 132-residue SEQ

ID NO:20 as recited instantly corresponds to a C-terminal fragment of full-length HM1.24 (SEQ ID NO:26), which contains 180 amino acids.

Therefore, although Goto et al. is silent with respect to the amino acid sequence of the HM1.24 antigen protein on the membranes of the RPMI 8226 cells, the specification indicates that the HM1.24 antigen on the cell membrane has the sequence of SEQ ID NO:26. Consequently, the evidence of record indicates that the Goto et al. protein necessarily is SEQ ID NO:26. Furthermore, Applicant has employed open transitional language in describing their invention ("a protein **having** the amino acid sequence..."), which means that the protein must include the recited sequence but may include additional amino acids on either end. As such, the full-length protein taught by Goto et al. reads on a protein "having" the amino acid sequence modified by lacking 17 amino acid residues from the C-terminal of SEQ ID NO:20 since it includes this sequence in addition to other amino acids on either end.

With respect to claims 7 and 13, Goto et al. employed a primary ^{125}I-labeled anti-HM1.24 antibody (see page 1924, right column).

26. Claim 2 is rejected under 35 U.S.C. 102(b) as being anticipated by Goto et al. as evidenced by Schimerlik as applied to claim 1 above, and further in light of the evidence of Kennel et al. ("Analysis of the Tumor-associated Antigen TSP-180" J Biol Chem. 1989 Sep 15;264(26):15515-21).

With respect to claim 2, the immunoprecipitation protocols of Goto et al. involved SDS-PAGE of the immunoprecipitated HM1.24 antigen followed by autoradiography procedures (see page 1924, "Immunoprecipitation" and Figure 5).

However, Goto et al. is silent as to whether such procedures involved binding the HM1.24 antigen to a solid support. The reference does not provide full experimental details regarding their protocols, but rather refer the reader to the non-patent literature publication by Kennel et al. (Citation No. 28 in Goto). See page 1924, "Immunoprecipitation", the last sentence of this section.

Kennel et al. is relied upon as an evidentiary reference disclosing additional experimental details of the immunoprecipitation and autoradiography procedures that were performed by Goto et al. In particular, Kennel et al. discuss separation of immunoprecipitated samples using SDS-PAGE followed by transferring of proteins onto a nitrocellulose membrane. Proteins on the membrane are then detected using a ^{125}I-labeled antibody by autoradiography. See page 15516, left column; and Figure 1.

Because Goto et al. explicitly refer to the publication by Kennel et al., it is clear that the procedures of Goto et al. also involved transfer of immunoprecipitated protein to a solid support (membrane) as part of their autoradiography experiments depicted in Figure 5. Therefore, in light of the evidence of Kennel et al., the teachings of Goto et al. anticipate the claim.

Claim Rejections - 35 USC § 103

27. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

28. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

29. Claims 1-2, 6-7, 13, and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Harlow & Lane (Harlow, E. and Lane, D., Antibodies: A Laboratory Manual (1988) Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, pages 555, 560-577, and 591-592) in view of Ishikawa et al. ("Molecular cloning and chromosomal mapping of a bone marrow stromal cell surface gene, BST2, that may be involved in pre-B-cell growth" Genomics. 1995 Apr 10;26(3):527-34), Gastinel et al. (U.S. 5,623,053), and Lauffer et al. (U.S. 5,639,597).

Harlow & Lane teach antibody-capture assays, in which an antigen is bound to a solid phase in order to capture specific antibody present within a test sample (see page 555, Figure 14.1 in particular; and pages 560 and 562-577). Such assays are useful, for example, in quantitating antibodies and can be used to compare the epitopes recognized by different antibodies (see especially at page 563, first paragraph).

Harlow & Lane therefore teach immunochemical assays of the same format as claimed instantly, in which an antigen is bound to a solid support and used to detect antibodies specific to the antigen in a test sample. However, Harlow & Lane fail to teach soluble HM1.24 antigen

protein as the type of antigen, and similarly fail to teach anti-HM1.24 antibodies as the type of antibodies detected.

Ishikawa et al. teach the antigen BST-2, which is a human membrane protein expressed on bone marrow stromal cells (the abstract). It is noted that BST-2 as taught by Ishikawa et al. is the same protein referred to in the instant specification as HM1.24 antigen. This is evident by referring to the predicted amino acid sequence for the 180-residue BST-2 protein in Figure 4 of Ishikawa et al., which is the same sequence disclosed instantly as SEQ ID NO:16 (the full-length human HM1.24 antigen). The authors conducted functional studies which suggested that this antigen may be involved in stimulating pre-B-cell growth (abstract; page 528, left column, first paragraph; page 531, right column, first sentence; and page 532, right column, last paragraph).

When taken together with the teachings of Harlow & Lane, therefore, it would have been obvious to one of ordinary skill in the art to pursue immunochemical antibody-capture assays using the novel BST-2/HM1.24 antigen taught by Ishikawa et al. as the type of antigen in order to detect antibodies specific to BST-2/HM1.24 in a test sample according to the methods of Harlow & Lane. One would be motivated to do this in order to quantify such antibodies and/or to compare their epitopes as part of experiments to further study a newly discovered protein of importance in pre-B-cell growth.

However, Ishikawa et al. further teach that the BST-2/HM1.24 protein is a transmembrane protein (the abstract).

Those of skill in the art at the time of the invention recognized certain technical considerations for dealing with antigens that are transmembrane proteins.

For example, Gastinel et al., in discussing the transmembrane FcRn receptor, teach that the hydrophobic nature of the receptor's transmembrane domain precludes the solubilization of the protein in aqueous buffer without the use of surfactants, which are often toxic, difficult to remove, and can reduce the stability of proteins (column 4, lines 43-50). As a result, the usefulness of the membrane-bound receptor is limited by the fact that, like other transmembrane proteins, is not readily soluble in aqueous solutions without surfactants (column 4, line 66 to column 5, line 2). By contrast, Gastinel et al. teach that there are many applications for an Fc receptor that is soluble in aqueous solutions without the use of a surfactant (column 4, lines 51-65; column 11, lines 62-67). Gastinel et al. further teach that such soluble receptors can be produced by removal of the transmembrane domain (column 5, lines 3-20; column 6, lines 1-10; column 10, lines 48-57). In addition, the soluble receptors of Gastinel et al. maintained the ability to bind to antibodies and can be attached to any compatible, functional surface (column 10, lines 42-47; column 11, lines 62-67).

Lauffer et al. discuss how binding experiments involving transmembrane receptor proteins can be carried out while the receptors remain bound to the cell, but that such assays are increasingly difficult as the number of receptors in the cell membrane decreases (column 1, lines 8-35). To avoid this drawback, Lauffer et al. propose receptor binding assays using soluble fusion proteins in place of membrane-bound receptors, in which the extracellular domains of human membrane proteins are fused to the constant part (Fc) of the heavy chain of an Ig (column 1, line 35 to column 2, line 40). Such fusion proteins retain their biological activity (column 1, lines 62-67). In addition, because the receptors are fused to Fc, they can be immobilized on a

solid phase (for example an ELISA plate) using rabbit serum specifically directed against the Fc constant region (column 2, lines 19-28).

The teachings of Gastinel et al. and Lauffer et al. indicate that those of skill in the art recognized certain technical obstacles that may arise when working with transmembrane proteins. In addition, the teachings of the references indicate that in order avoid such obstacles, it was known to use soluble forms of such transmembrane proteins (for example, soluble receptor-Fc fusion proteins) in place of the full-length, membrane-bound proteins.

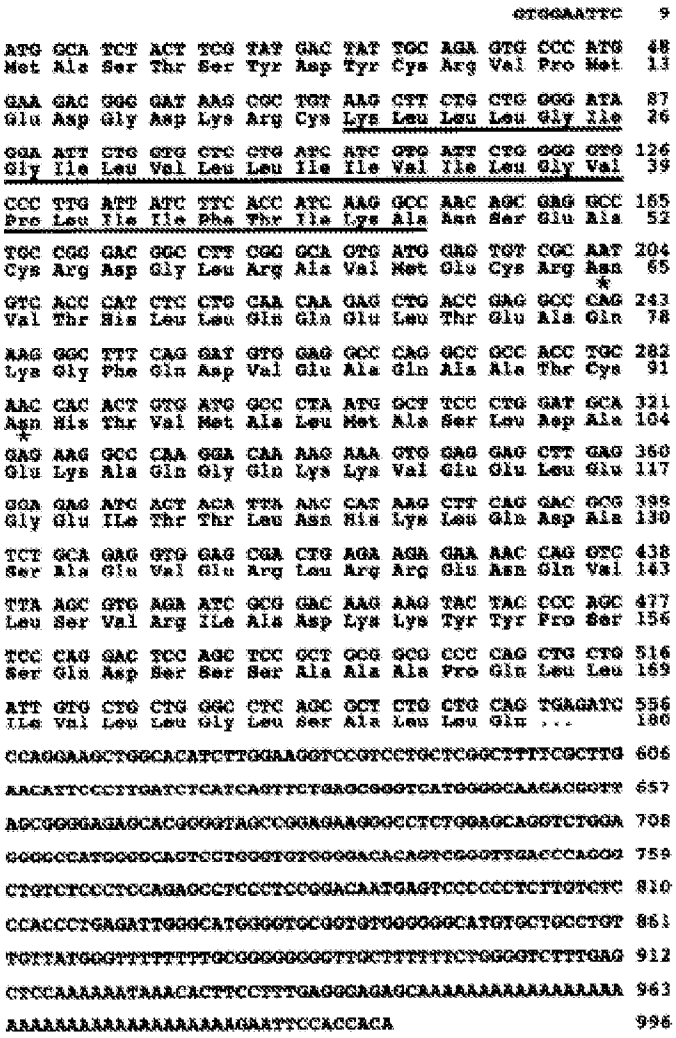
In addition to identifying BST-2/HM1.24 as a transmembrane protein, Ishikawa et al. (discussed above) also constructed a soluble form of BST-2/HM1.24, in which the putative extracellular region of was fused to the Fc region of human IgG1 (see page 527, right column, "Production of soluble recombinant BST-2/HM1.24-immunoglobulin fusion protein"; and also at page 530, left column, first paragraph; and Figure 4).

When taken together with the teachings of Gastinel et al. and Lauffer et al., therefore, it would have been obvious to one of ordinary skill in the art to employ a soluble form of the BST-2/HM1.24 antigen when performing antibody-capture assays for anti-HM1.24 antibodies according to the method of Harlow & Lane and Ishikawa et al. One would be motivated to use a soluble form instead of the full-length antigen because to avoid potential technical problems known to arise when using full-length transmembrane receptors.

With respect to the limitation that the soluble HM1.24 antigen protein used in the method is one “having the amino acid sequence modified by lacking 17 amino acid residues from C-terminal in the amino acid sequence showin in SEQ ID NO:20”, the Examiner notes that the soluble BST-2/HM1.24-immunoglobulin fusion protein taught by Ishikawa et al. corresponds to

the portion of HM1.24 from asparagine 49 to serine 162 (see page 527, right column, "Production of soluble recombinant BST-2/HM1.24-immunoglobulin fusion protein"; and also at page 530, left column, first paragraph; and Figure 4). Comparing the sequence information in Figure 4 of Ishikawa et al. with instant SEQ ID NO:20, it can be seen that the sequence Asn 49 to Ser 162 corresponds to the amino acid sequence shown in SEQ ID NO:20, but lacking the last 18 amino acids of SEQ ID NO:20.

Figure 4 of Ishikawa:



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                                                        GTGGAATTC    9

ATG GCA TCT ACT TCG TAT GAC TAT TGC AGA GTG CCC ATG   48
Met Ala Ser Thr Ser Tyr Asp Tyr Cys Arg Val Pro Met   13

GAA GAC GGG GAT AAG CGC TGT AAG CTT CTG CTG GGG ATA   87
Glu Asp Gly Asp Lys Arg Cys Lys Leu Leu Leu Gly Ile   26

GGA ATT CTG GTG CTC CTG ATC ATC GTG ATT CTG GGG GTG 126
Gly Ile Leu Val Leu Leu Ile Ile Val Ile Leu Gly Val   39

CCC TTG ATT ATC TTC ACC ATC AAG GCC AAC AGC GAG GCC 165
Pro Leu Ile Ile Phe Thr Ile Lys Ala Asn Ser Glu Ala   52

TGC CGG GAC GGC CTT CGG GCA GTG ATG GAG TGT CGC AAT 204
Cys Arg Asp Gly Leu Arg Ala Val Met Glu Cys Arg Asn   65
                                                  *

GTC ACC CAT CTC CTG CAA CAA GAG CTG ACC GAG GCC CAG 243
Val Thr His Leu Leu Gln Gln Glu Leu Thr Glu Ala Gln   78

AAG GGC TTT CAG GAT GTG GAG GCC CAG GCC GCC ACC TGC 282
Lys Gly Phe Gln Asp Val Glu Ala Gln Ala Ala Thr Cys   91

AAC CAC ACT GTG ATG GCC CTA ATG GCT TCC CTG GAT GCA 321
Asn His Thr Val Met Ala Leu Met Ala Ser Leu Asp Ala 104
 *

GAG AAG GCC CAA GGA CAA AAG AAA GTG GAG GAG CTT GAG 360
Glu Lys Ala Gln Gly Gln Lys Lys Val Glu Glu Leu Glu 117

GGA GAG ATC ACT ACA TTA AAC CAT AAG CTT CAG GAC GCG 399
Gly Glu Ile Thr Thr Leu Asn His Lys Leu Gln Asp Ala 130

TCT GCA GAG GTG GAG CGA CTG AGA AGA GAA AAC CAG GTC 438
Ser Ala Glu Val Glu Arg Leu Arg Arg Glu Asn Gln Val 143

TTA AGC GTG AGA ATC GCG GAC AAG AAG TAC TAC CCC AGC 477
Leu Ser Val Arg Ile Ala Asp Lys Lys Tyr Tyr Pro Ser 156

TCC CAG GAC TCC AGC TCC GCT GCG GCG CCC CAG CTG CTG 516
Ser Gln Asp Ser Ser Ser Ala Ala Ala Pro Gln Leu Leu 169

ATT GTG CTG CTG GGC CTC AGC GCT CTG CTG CAG TGAGATC 556
Ile Val Leu Leu Gly Leu Ser Ala Leu Leu Gln ...      180

CCAGGAAGCTGGCACATCTTGGAAGGTCCGTCCTGCTCGGCTTTTCGCTTG 606

AACATTCCCTTGATCTCATCAGTTCTGAGCGGGTCATGGGGCAACACGGTT 657

AGCGGGGAGAGCACGGGGTAGCCGGAGAAGGGCCTCTGGAGCAGGTCTGGA 708

GGGGCCATGGGGCAGTCGTGGGTGTGGGGACACAGTCGGGTTGACCCAGGG 759

CTGTCTCCCTCCAGAGCGTCCCTCCGGACAATGAGTCCCCCCTCTTGTCTC 810

CCACCCTGAGATTGGGCATGGGTCCGGTGTGGGGGGCATGTGCTGCCTGT 861

TGTTATGGGTTTTTTTTGCGGGGGGGGTTGCTTTTTTCTGGGGTCTTTGAG 912

CTCCAAAAAAATAAACACTTCCTTTGAGGGAGAGCAAAAAAAAAAAAAAAAA 963

AAAAAAAAAAAAAAAAAAAAGAATTCCACCACA                    996
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FIG. 4. Nucleotide and predicted amino acid sequence of human BST-2 cDNA. The putative transmembrane region is underlined. Two potential sites of N-linked glycosylation are indicated by asterisks. This sequence data have been deposited with DDBJ/EMBL/GenBank under Accession No. D28137.

SEQ ID NO:20 as disclosed instantly:

<210> 20
<211> 132
<212> PRT
<213> Homo sapiens

<220>
<223> Amino acid sequence of soluble HM 1.24 antigenic protein

<400> 20
Asn Ser Glu Ala Cys Arg Asp Gly Leu Arg Ala Val Met Glu Cys Arg
1 5 10 15

Asn Val Thr His Leu Leu Gln Gln Glu Leu Thr Glu Ala Gln Lys Gly
20 25 30

Phe Gln Asp Val Glu Ala Gln Ala Ala Thr Cys Asn His Thr Val Met
35 40 45

Ala Leu Met Ala Ser Leu Asp Ala Glu Lys Ala Gln Gly Gln Lys Lys
50 55 60

Val Glu Glu Leu Glu Gly Glu Ile Thr Thr Leu Asn His Lys Leu Gln
65 70 75 80

Asp Ala Ser Ala Glu Val Glu Arg Leu Arg Arg Glu Asn Gln Val Leu
85 90 95

Ser Val Arg Ile Ala Asp Lys Lys Tyr Tyr Pro Ser Ser Gln Asp Ser
100 105 110

Ser Ser Ala Ala Ala Pro Gln Leu Leu Ile Val Leu Leu Gly Leu Ser
115 120 125

Ala Leu Leu Gln
130

Therefore, Ishikawa et al. disclose a soluble HM1.24 antigen protein having the amino acid sequence modified by lacking 18 amino acid residues from the C-terminus of SEQ ID NO:20, while the instantly claimed invention recites a protein modified by lacking 17 amino acid residues from the C-terminus of SEQ ID NO:20. In other words, the instant claims invoke proteins comprising the sequence from amino acids 49 to 163 of full-length HM1.24, while the soluble HM1.24 antigen protein of Ishikawa et al. ranges from amino acids 49 to 162. The Ishikawa et al. protein is missing an additional residue from the C-terminus, namely the alanine residue at position 163 of the full-length protein.

However, the courts have ruled that in the case where the claimed ranges "overlap or lie inside ranges disclosed by the prior art" a prima facie case of obviousness exists. See MPEP 2144.05.

In the instant case, the teachings of Gastinel et al. and Lauffer et al. establish that deleting amino acids from a transmembrane protein was known to have effects on the physical properties of the protein, namely on the protein's solubility. Lauffer et al. further contemplate soluble fusion proteins composed of "various portions of the extracellular domains of human membrane proteins" (column 1, lines 46-56). Such teachings indicate that the particular amino acids sequence of a transmembrane receptor was known to be a result-effective variable.

Therefore, it would have been obvious to one of ordinary skill in the art to vary the amino acid sequence of the soluble HM1.24 antigen protein of Ichikawa et al. by including an additional amino acid at the region corresponding to the C-terminus of HM1.24. In particular, because Ishikawa et al. taught that the next amino acid in the endogenous sequence of HM1.24 is alanine 163, it would have been obvious to include this residue in the construct. Put another way, it would have been obvious to remove 17 rather than 18 amino acids from the C-terminus of HM1.24 when preparing the soluble HM1.24 antigen protein.

Furthermore, when taken together with the general knowledge in the art that the amino acid alanine is a small amino acid that possesses no reactive groups on its side chain, one would have had a reasonable expectation of success including alanine 163 in the soluble HM1.24 antigen protein of Ichikawa et al. because the resulting protein lacking 17 rather than 18 amino acids would be reasonably expected to have the same properties.

In addition, one of ordinary skill in the art would have had a reasonable expectation of success in using the modified soluble HM1.24 antigen protein of Ichikawa et al. to detect anti-HM1.24 antibodies according to the antibody-capture assay format of Harlow & Lane based on the teachings of Gastinel et al. that soluble receptors maintained the ability to bind to antibodies. Similarly, Lauffer et al. taught that soluble fusion protein of transmembrane receptors retain their biological activity.

It is also possible to analyze the teachings of Ichikawa et al. in view of those of Harlow & Lane, Gastinel et al., and Lauffer et al. In particular, although Ichikawa et al. do not specifically direct the skilled artisan to employ the soluble HM1.24 antigen protein for the purpose of detecting anti-HM1.24 antibodies, known uses for antigens included using solid-phased antigen for the purpose of detecting cognate antibodies in immunochemical assays, as taught by Harlow & Lane. Further, it was known to use soluble forms of transmembrane receptors in place of full-length membrane-bound forms for technical reasons, as taught by Gastinel et al. and Lauffer et al. Finally, although the soluble HM1.24 antigen protein of Ichikawa et al. lacks 18 rather than 17 amino acids from the C-terminus of SEQ ID NO:20, based on the knowledge of the amino acid sequence of HM1.24 as taught by Ichikawa et al. as well as the general knowledge in the art, one would reasonably expect the two proteins to possess the same properties.

With respect to claim 2, Harlow & Lane teaches binding antigens to a solid phase as discussed above. One would have had a reasonable expectation of success in binding the soluble HM1.24 antigen protein to a solid phase because Gastinel et al. taught that soluble receptors could be attached to any compatible, functional surface (column 10, lines 42-47; column 11, lines 62-67).

With respect to claim 6, Harlow & Lane teaches immobilization of antigens for the antibody-capture assay on microtiter plates (page 563, second paragraph).

With respect to claim 7, Harlow & Lane teaches using a secondary labeled reagent that will specifically recognize the antibody (i.e., a primary antibody against the antibody). See page 563, first paragraph and page 564. Therefore, when conducting antibody capture assays using soluble HM1.24 antigen protein to detect anti-HM1.24 antibodies as discussed above, it would have been further obvious to employ a labeled reagent that specifically recognized anti-HM1.24 antibodies in order to detect antigen-antibody binding.

With respect to claim 13, Harlow & Lane discuss how all immunoassays rely on labeled reagents for detection (pages 591-592). Suitable labels include radioactive compounds, enzymes, biotin, or fluorochromes (page 591, first paragraph).

30. Claims 8-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Harlow & Lane in view of Ishikawa et al., Gastinel et al., Lauffer et al., as applied to claim 1 above, and further in view of Frank et al. (U.S. 5,646,115).

The references are as discussed in detail above. Harlow & Lane teaches antibody-capture immunochemical assays in which binding of antibody in a test sample to solid phase antigen is detected using an antibody specific to the test antibody. However, the references fail to specifically teach using a second antibody in addition to the antibody specific to the test antibody.

Frank et al. teach immunochemical assays in which antigen (saliva proteins) are immobilized on a solid phase and used to capture antibodies in a body fluid test sample (column

34, line 22 to column 35, line 45). The reference teaches that the amount of antibody bound to the solid phase can be determined using one or more layers of secondary antibodies. For example, an untagged secondary antibody can be bound to a serum antibody (in the test sample) and the untagged secondary antibody can then be bound by a tagged tertiary antibody). See column 35, lines 35-45.

Therefore, it would have been further obvious to one of ordinary skill in the art to employ a second antibody (tagged tertiary antibody) as taught Frank et al. in addition to the primary antibody taught by Harlow & Lane in the method of Harlow & Lane, Ishikawa et al., Gastinel et al., and Lauffer et al. in order to achieve the same purpose, namely that of determining the amount of antibody in the test sample that is bound to the solid phase. More particularly, one would be motivated to include an additional antibody layer in this manner in order to determine the amount of anti-HM1.24 antibody in a test sample.

Response to Arguments

31. Applicant's arguments in the Reply filed 10/18/207 have been considered but are moot in view of the new ground(s) of rejection.

Conclusion

32. The following art made of record and not relied upon is considered pertinent to applicant's disclosure. Information Hyperlinked over Proteins (iHOP), entry for BST2, retrieved from http://www.ihop-net.org/UniPub/iHOP/gs/86791.html on 4/9/09 provide additional

evidence that the BST-2 protein as disclosed by Ishikawa is the same as the HM1.24 antigen disclosed instantly (see "Synonyms").

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christine Foster whose telephone number is (571) 272-8786. The examiner can normally be reached on M-F 6:30-3:00. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mark Shibuya can be reached at (571) 272-0806. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Christine Foster/
Examiner, Art Unit 1641

/Christopher L. Chin/
Primary Examiner, Art Unit 1641